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Cow's Milk Desensitization in Anaphylactic Patients: A New Personalized-dose Method

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ABSTRACT

Cow's milk allergy (CMA) is the most frequent food allergy in children and oral immunotherapy (OIT) is a promising approach for treatment of patients. The most challenging cases are anaphylactic with coexisting asthma and proposing safe protocols is crucial especially in high risk groups. Considering that CMA varies among patients, an individualized OIT protocol would be beneficial to achieve a safer and more efficient method of desensitization.

18 children more than 3 years of age with IgE-mediated CMA were enrolled. CMA was confirmed by positive skin prick test (SPT) and positive oral food challenge (OFC) and 60% of individuals had a convincing history of persistent asthma. SPT with milk extracts, whole fresh milk and serially diluted milk concentrations were performed. The dilution of milk that induced 3-5 mm of wheal in each individual was selected as the starting dilution for OIT. Desensitization began by 1 drop of the defined dilution and continued increasingly.

Overall, 16 out of 18 children (88.8%) achieved the daily intake of 120 mL of milk. Four out of these 16 children accomplished the protocol without any adverse allergic reactions. 12 patients experienced mild to severe reactions. Wheal and erythema in SPT ($p \leq 0.001$), and sIgE ($p \leq 0.003$) to most milk allergens were significantly decreased following desensitization.

We successfully desensitized 16 of 18 children with IgE-mediated CMA by individualized desensitization protocol. Individualizing the OIT protocol would be helpful to save time and perhaps to relieve the allergic symptoms after ingesting cow's milk intake.

Keywords: Anaphylaxis; Cow's milk allergy; Desensitization; Immunologic; OIT; Oral tolerance

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INTRODUCTION

Milk allergy is the most common food allergy in children (both IgE- and non-IgE-mediated hypersensitivities). It can be severe particularly in those having a positive history of anaphylaxis to milk and a higher level of specific immunoglobulin E (sIgE).[1] Most infants with non-IgE-mediated cow's milk allergy (CMA) outgrow their sensitivity by the age of three,[2,3] While 10% to 25% of infants with IgE-mediated CMAs keep their sensitivity into second decade. Some studies have shown that only 19% of milk allergies are alleviated by the age of 4 and about 80% by the age of 16 years.[4,5]

The basic treatment for the milk allergy has been an elimination diet and waiting for natural tolerance. This treatment is effective in some cases; however, elimination diet for a long period of time may result in malnutrition, eating disorders, and other psychological problems.[6-9] Therefore dietary or pharmaceutical supplementation is advised for these patients.[10] Aside from avoidance, active disease-modifying therapy for food allergy has been studied in recent years and several reports have emerged on milk oral immunotherapy (OIT), or using heated products of milk or egg, in patients with severe reactions to cow's milk (CM) protein.[5,11-13] However, data on the efficacy, safety, course and long-term outcome, especially in asthmatic patients are limited.[14]

Since the introduction of oral tolerance,[15] the exact immunological mechanism of OIT is not fully understood,[16,17] but it has been more studied recently due to severe systemic reactions following traditional type of immunotherapy.[5.18,19] OIT is becoming an increasingly common treatment for food allergies. It usually contains two phases: build up and maintenance. The former could be slow (conventional) or fast (rush) until the target dose is achieved. The latter involves daily consumption of the final dose.[5,6,20]

There are so many factors affecting the efficacy of OIT such as the schedule of immunotherapy, severity of anaphylaxis, presence of other risk factors like asthma, age of desensitization. On the other hand the factors affecting the efficacy of OIT are complicated and dependent on patients' immune system. Most of protocols have a same manner for all patients, without any personal modification in doses. Therefore, we designed this trial to recruit patients with CM anaphylaxis to achieve a personalized, safe and efficient oral desensitization protocol, especially in patients with concurrent asthma.

PATIENTS AND METHODS

Patients over than 3 years of age, with a convincing history of anaphylaxis to CM and positive skin prick test (SPT) confirmed by positive oral food challenge (OFC) were admitted to the OIT trial. Trial started 2 months after the last anaphylaxis to milk. Patients with underlying cardiopulmonary disorders, uncontrolled asthma, any significant systemic disease, and poor compliance were excluded from the study. Among 25 children, 18 were recruited in Rasool-e-Akram Hospital, Tehran, Iran University of Medical Sciences and Mofid Children's Hospital, Tehran, Shahid Beheshti University of Medical Sciences from June 2013 to the end of 2014. Five children were excluded because of unstable asthma and two due to uncontrolled seizures. 18 patients were recruited

A detailed clinical history including: sex, age, family and personal history of allergies, symptoms after previous ingestion of CM was taken and a written informed consent was collected. SPT with some commercial common inhalant allergens including, mite mixture, alternaria, tree mix, grass mix, weed mix, and food allergens including peanut, walnut, hazelnut, egg, wheat, soy and fish mix (Greer, USA) was done. Histamine (1:1.000) and glycerine were used as positive and negative controls, respectively. Prick to prick was also performed by applying 1 drop of fresh milk and 1:10, 1:25, 1:50, 1:100, 1:200, 1:400, and 1:500 milk dilutions. In addition to SPT, CM, α lactoalbumin, β lactoglobulin, casein, and bovine serum albumin specific IgEs were measured using an immunoblotting method (R-biopharm, Darmstadt, Germany).

Milk Desensitization Protocol

SPT with the milk extract and dilutions of fresh milk were done for all recruited patients. The dilution of milk that induced 3-5 mm of wheal was selected as the starting dilution for each individual and we started with one drop of the determined dilution. In the first session the CM doses were doubled every 15 minutes up to 16 drops, and then it was continued through the next week. In the second week, the previous dose was increased two-folded and continued through the week. The dilution of milk was changed

biweekly according to the protocol (Table 1), in order to achieve a total daily intake of 120 mL. If any symptoms such as common cold, viral diarrhea, fever, etc. were observed during the oral desensitization, the dose was not increased and the previous dose was repeated. No ingestion of CM was allowed out of the scheduled protocol. All the new doses were administered under medical supervision in a clinical setting. 30 minutes after receiving each dose, patients were carefully assessed for positive reactions. Mild reactions were managed by antihistamines and severe reactions and anaphylaxis were managed by epinephrine, steroid, and antihistamine. Patients who developed moderate to severe reactions were observed at least 4 h in emergency department or admitted if needed. In case of anaphylaxis, the applying dose returned to the previous tolerated dose for one week and then it was increased by half of the last one. This protocol was approved by medical ethics committee in Shahid Beheshti University of Medical Sciences and was registered in Iranian Registry of Clinical Trials (IRCT) with the following identifier: IRCT2013080814305N1.

Blood Samples

Venous blood samples were collected at the beginning of the protocol and after desensitization to determine sIgEs against milk and its components. Total serum IgE, using an immunoblotting method (R-biopharm, Darmstadt, Germany), and absolute eosinophil count were measured as well.

Statistical Analysis

Statistical analyses were performed using SPSS 16 software (IBM Corp., Armonk, N.Y., USA). Mean, standard deviation, and median were used for descriptive quantitative data, and frequency was used for analysis of qualitative data. Paired T-test was used for the comparison of wheal and flare sizes before and after OIT. Logistic regression was used to evaluate the effect of risk factors (food or aeroallergen sensitization, past medical history and/or family history of atopy, and current asthma or other allergic disorders) on the success of the protocol. sIgE levels before and after OIT was compared by non-parametric Wilcoxon signed rank test. A p value ≤ 0.05 was considered significant for all comparisons.

RESULTS

18 patients were recruited to the study, 11 males (61%), and 7 females (38.9%), ranged from 3 to 19 years (Mean=6.9). 11 of the 18 children (≈68%) suffered from asthma, 8 (≈44%) from allergic rhinitis, and 3(≈11%) from urticaria. All of the patients had a positive history of allergic diseases in their infancy. SPT revealed sensitization against aeroallergens (including mite, alternaria, tree mix, grass mix, and weed mix) in 7 patients (41.2%), eggs in 8 patients (41.7%), and nuts in 5 patients (29%). Mean total IgE of patients was 177 KIU/L (ranged from 26 to 400) and mean of absolute eosinophil count was 414 cell/μL (ranged from 0-1250).

Table 1. Time table of oral immunotherapy **using cow's milk**

Week of visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
Dilution of milk	1:500*		1:400*		1:200*		1:100*		1:50*		1:25*		1:10*		Full dilution of milk							
Drops ingested	2	16	5	10	5	10	5	10	5	10	5	10	5	10	5*	2¶	4	8	16	32	64	120
Each 15 minute	2	16	5	10	5	10	5	10	5	10	5	10	5	10	5							
	4														10							
	8																					
Total dose during each week	16	32	10	20	10	20	10	20	10	20	10	20	10	20	20	2	4	8	16	32	64	120

*drops, ¶milliliter of milk

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Table 2. Age, sex, starting dilution, symptoms during cow's milk (CM) desensitization, treatment, and outcome of the desensitization protocol

Patient ID	Age	Sex	Starting Dilution	Outcome of desensitization	Symptoms during CM desensitization	Dose of CM when symptoms intervened	Treatment
1	3.00	M	1:400	120cc	Wheezing, Urticaria	20gtt* 1:200	Epinephrine +Steroid+ Antihistamine
					Vomiting, Wheezing	10gtt 1:50	Epinephrine +Steroid+ Antihistamine
					Uricaria, Cough	32cc Full	Epinephrine +Steroid+ Antihistamine
2	11.00	M	1:400	120 cc	Wheezing, Urticaria, Vomiting	16 cc Full	Epinephrine +Steroid+ Antihistamine
3	3.00	M	1:200	120 cc	Vomiting, Wheezing, Urticaria	20gtt 1:100	Epinephrine +Steroid+ Antihistamine
					Uricaria, Abdominal pain	16cc Full	Epinephrine +Steroid+ Antihistamine
4	3.00	M	1:100	120 cc			
5	4.00	M	1:400	120 cc			
6	3.00	M	1:400	120 cc	Wheezing, Cough, urticaria	20gtt 1:10	Epinephrine +Steroid+ Antihistamine
7	3.00	M	1:500	120 cc	Wheezing, Urticaria	10gtt Full	Epinephrine +Steroid+ Antihistamine
					Abdominal pain, wheezing	16 cc Full	Epinephrine +Steroid+ Antihistamine
					Urticaria	32 cc Full	Antihistamine
					Uricaria, Cough, Hoarsness	64cc Full	Epinephrine +Steroid+ Antihistamine
8	19.00	F	1:400	120 cc	Abdominal Discomfort	16cc Full	Antihistamine
9	4.00	F	1:400	120 cc	Wheezing, Sneezing, Agitation, Rhinorrhea	32cc Full	Epinephrine +Steroid+ Antihistamine
					Abdominal pain, Urticatia	64 cc Full	Epinephrine +Steroid+ Antihistamine
10	5.00	F	1:10	120 cc			
11	4.00	F	1:200	120 cc	Flushing, Urticaria, Cough,	20gtt 1:50	Epinephrine +Steroid+ Antihistamine
					Pallor, Wheezing, Cough	10gtt 1:10	Epinephrine +Steroid+

					Cough attack, Hoarseness	64cc	Full	Antihistamine Epinephrine +Steroid+ Antihistamine
12	13.00	M	1:25	120 cc				
13	5.00	M	1:400	120 cc	Mouth itching	8cc	Full	Antihistamine
14	3y	F	1:400	Discontinue at 64 cc of Full				
15	7y	F	1:500	Discontinue At 16cc of full	Mouth itching, Vomiting, Urticaria	20gtt	1:200	Epinephrine +Steroid+ Antihistamine
					Hoarseness, Urticaria, Wheeze	2c c	Full	Epinephrine +Steroid+ Antihistamine
					Wheeze, Abdominal pain, Urticaria	4cc	Full	Epinephrine +Steroid+ Antihistamine
					Wheeze, Cough, Urticaria	16cc	Full	Epinephrine +Steroid+ Antihistamine
					Wheeze, Oral Itching, Urticaria	16cc	Full	Epinephrine +Steroid+ Antihistamine
16	13y	M	1:50	120 cc	Urticaria	32cc	Full	Antihistamine
17	9	F	1:200	120 cc	Mouth and lip itching	16cc	Full	Antihistamine
18	12y	M	1:10	120 cc		120cc	Full	

*gtt: drops

Desensitization started from the 1:400 dilution of milk in 44% of patients and 1:200 in 16.7% of patients. The period of desensitization varied between 10 to 27 weeks. Overall, 16 of the 18 children (88.8%) achieved the daily intake of 120 mL of milk (Table 2). Among these children, four accomplished the protocol without showing any symptoms, and 12 presented moderate to severe symptoms (Table 1). Totally, 498 doses were administered and 21 episodes of anaphylaxis happened during this trial, and the mean number of anaphylaxis was 1.17 (median=0.5). Nine patients achieved 120 cc of full milk without any anaphylaxis. We did not find any significant correlation between aeroallergen or food sensitization, PMH or family history of atopy, coexisting of an allergic disorders and the number of anaphylaxis during desensitization (data not shown, $p>0.05$). One of the patients (No.15) quitted the protocol because of several severe anaphylaxis and serious asthma exacerbations. Of note, Patient No.14 developed recurrent abdominal pain and after endoscopy and biopsy was diagnosed as eosinophilic esophagitis (EoE). All of the other tolerant patients were followed 1 year after OIT and were able to consume more than 120 cc of milk and other dairy products in a day.

The mean ±SD size of wheal in SPT before OIT (12±5.1 mm) significantly decreased to 5.83±3.34 mm after desensitization ($p\leq0.001$, CI 95%; 3.2-9). Also, data showed significant reduction of erythema following SPT after desensitization ($p=0.001$, CI95%; 7-20.9) (Table 3). The mean and interquartile range (IQR) for the levels of serum specific IgE against milk and its components (casein, α lactalbumine, β lactoglobuline, and serum bovine albumin) before and after desensitization is shown in Table 4. As shown, a significant decrease in specific IgE level against milk and its components, except serum bovine albumin was observed.

Table 3. Outcome of the point skin prick tests (SPTs) with milk extract at the beginning, and at the end of the oral immunotherapy

	Before desensitization	After desensitization	change	*p* value
	Mean (mm)	Mean (mm)		
Skin prick test Wheal	12±5.1*	5.83± 3.34	6.1 (3.2-9)¶	0.000
Skin prick test Erythema	24.61±8.51	12.27± 7.93	14 (7-20.9)	0.001

* Mean ± Std. Deviation

¶95% Confidence interval of the difference

Table 4. Results of specific IgE levels against whole cow's milk, casein, α-lactoalbumin, β lactoglobuline, and serum bovine albumin, before and after the oral desensitization

	Before desensitization		After desensitization		*p*-value
	Mean (IU/mL)	IQR	Mean (IU/mL)	IQR	
sIgE to whole milk	3.1875	1.75	2.3125	1	0.003
sIgE to α lactoalbumin	3.1333	1	2.6000	1	0.020
sIgE to βlactoglobuline	3.3750	1	2.3125	1.75	0.014
sIgE to Casein	3.3125	1	2.3750	1	0.019
sIgE to serum Bovine albumin	1.7143	3	1.7692	3.3	0.705

DISCUSSION

In this study we described a new personalized desensitization protocol for treatment of cow's milk anaphylaxis. We specifically chose the starting dilution for each patient, then gradually increased doses or changed the dilutions. Due to different starting doses the period of desensitization ranged between 10 to 27 weeks. The overall success rate of OIT was 88.8%, meaning that 16 patients could intake at least 120 mL of milk per day. The success rate of our trial with respect to the severity of adverse allergic reactions in patients with CM anaphylaxis was considerable. Despite precautions taken by patients and their families, incidental ingestion of milk via processed foods may cause severe anaphylactic reaction and affect the quality of life.[21] Consequently, efforts have been made to substitute the elimination diet with desensitization or tolerance induction modalitis.

According to the BSACI Guidelines,[22] regarding milk allergy, wheal size equal or more than 5 mm (≥2 mm in younger infants) after SPT is strongly predictive for allergy to CM proteins. Therefore, reduced wheal and flare in our patients after desensitization confirm their clinical response and could be indicative of tolerance induction. As data shown here, wheal and erythema reactions following SPT were significantly decreased in patients after OIT with CM.

There are some experiences about milk OIT. Skripak et al., reported a randomized OIT to milk or placebo in 20 children, according to a 3-phase protocol. They started from 0.4 mg of milk protein and reached to 50 mg daily.[23] Zapatero et al.,[24] desensitized 18 children older than 4 years with CM protein allergy, 89% of patients achieved a tolerance with 200-250 mL of milk in a day. Meglio et al.,[6] published a desensitization protocol that began with 1 drop of a 1:25 dilution of milk increasing to 200 mL on day 180 (6^{th} months). 71.4% of patients achieved the final dose, while some of them were partially tolerant. Bauer et al.[25] reported a rapid oral desensitization in a 12-year-old girl, using 0.01 mL of milk then increasing two-folded until 200 mL on day 5 after desensitization. Staden et al.,[10] reported a desensitization protocol for induction of tolerance in 9 children over 3 years of age. They started from 1:100 of the eliciting dose, and then a two-folded increased dose was administered after 2 h with 3 to 5 doses in a day. Doses were increased up to 120 mL of CM. Patriarca et al.[11] began their OIT protocol with 1 drop of milk and increased it up to 120 mL over a period of 136 days. From 16 children enrolled in that study, 13 (76.9%) completed the

desensitization in 3-12 months, while 3 had to quit the trial due to severe adverse effects.

In our study 16 of the 18 participating patients (89%) achieved a tolerance to 120 mL of cow's milk a day, and we used personalized starting dose based on SPT. Six patients under 4 years of age finished the protocol successfully; therefore, it seems that starting OIT in children over 3 years was effective and decreased the chance of anaphylactic reactions after accidental exposure to allergens. Our finding was similar to Meglio et al.'s and Bauer et al.'s studies, who demonstrated promising results after OIT therapy in atopic patients.[6,25] In contrast to other studies, we started the desensitization based on patient's SPT results, so the dose and duration of protocol varied among patients. Individualizing the desensitization protocol is a safe and time saving method. We had 11 asthmatic patients in our trial (68%), but the rate of anaphylaxis was similar to other studies and only one of them could not accomplish the protocol. During the study we observed 21 episodes of anaphylaxis among 498 administered doses, the mean number of episodes were 1.17 (median=0.5). The likelihood of accidental exposure in preschool-aged children has been determined as 71% in 3-year period and approximately 11% of them graded as severe anaphylaxis.[26] However, in milk OITs like ours, rate of anaphylaxis is less than natural exposures.[3,11,12,16,26] Of note, we did not find any significant correlation between risk factors such as aeroallergen and the number of anaphylaxis, in contrast to a review by Elizur et al. that reported asthma as a risk factor for severe anaphylaxis and a threat to OIT efficacy.[14] During the trial one other patient failed to finish the protocol due to abdominal pain, after evaluation she was diagnosed as EoE. Maggadottir et al. showed development of EoE in children after OIT treatment,[9] which was found in our patient as well. Our current understanding from EoE pathogenesis suggest that disease occurrence is not related to IgE-mediated food allergy, although both may arise concurrently in the same individual. Some studies have proposed that some premedications like cromoglycate acid or cetirizine are necessary to decrease allergy symptoms during OIT treatment decrease allergy.[5,6] Omalizumab has been successfully experienced in cases with refractory anaphylaxis in tolerance induction protocols.[27] Although a large number of evidence show the successful results of OIT, there are some concerns about the future of OIT. It is worth noting that to date, our patients have tolerated cow's milk, 1 year after the desensitization procedure. However, further follow up and challenge would be valuable.

We indicated that serum sIgE to milk, casein, α-lactalbumine, and β- lactoglobuline, had significantly decreased after desensitization. However, Zapatero et al just could show reduced IgE against casein in response to desensitization treatment.[24] In our study, we could not predict outcome of OIT treatment in our patients based on their SPT and specific IgE results. It needs more investigation, as currently we are recruiting more patients to the similar study

In this study, we successfully used personalized dose desensitization protocol for patients with cow's milk anaphylaxis. It should be noted that although concerns regarding the safety of OIT and its long term efficacy remains, food desensitization treatment has opened a new window to the future of food allergy treatment. We propose that personalizing the milk desensitization protocol is an effective and reasonably safe method; moreover, it save time and improve patients' cooperation. Further studies should be done to determine the optimum time of intervention for treatment of patients suffering from food allergies.

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